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Combined proportional and additive residual error models in population pharmacokinetic modelling

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ABSTRACT

Introduction: In pharmacokinetic modelling, a combined proportional and additive residual error model is often preferred over a proportional or additive residual error model. Different approaches have been proposed, but a comparison between approaches is still lacking.
Methods: The theoretical background of the methods is described. Method VAR assumes that the variance of the residual error is the sum of the statistically independent proportional and additive components; this method can be coded in three ways. Method SD assumes that the standard deviation of the residual error is the sum of the proportional and additive components. Using datasets from literature and simulations based on these datasets, the methods are compared using NONMEM.
Results: The different coding of methods VAR yield identical results. Using method SD, the values of the parameters describing residual error are lower than for method VAR, but the values of the structural parameters and their inter-individual variability are hardly affected by the choice of the method.
Conclusion: Both methods are valid approaches in combined proportional and additive residual error modelling, and selection may be based on OFV. When the result of an analysis is used for simulation purposes, it is essential that the simulation tool uses the same method as used during analysis.

1. Introduction

Selecting the appropriate residual error (also denoted residual unexplained variability) model is an important step in population pharmacokinetic and pharmacodynamic modelling (Dosne et al., 2016). In pharmacokinetic modelling, a combined proportional and additive residual error model is often found to describe the data better than a proportional or additive error model, as can be concluded from many publications. Moreover, this model is logical from a theoretical point of view, with a proportional component related to the proportional relationship between concentration and instrumental response in bioanalysis, as well as an additive component, among others related to instrumental noise level, resulting in a lower limit of quantification. For other sources of residual error, e.g. model misspecification, the relationship between concentration and residual error is less obvious. A general framework for residual error modelling incorporating scedasticity of variance and distribution shape was published recently (Dosne et al., 2016).

Little attention has been paid in literature to the fact that the combined residual error model can be modelled in different ways. The existence of different approaches has been discussed in discussion groups (NONMEM Users Network, 2001; PharmPK Discussion, 2013), but a comparison between these approaches is still lacking.

It is the aim of this paper to show the background of methods for combined proportional and additive residual error modelling, to compare the results obtained with different methods, and to discuss the impact of the methods.

2. Methods

2.1. Residual Error Models

The combined proportional and additive residual error model can be implemented in different ways, dependent on the assumption about the mathematical relationship describing the variance or standard deviation of the residual error:

- Method VAR assumes two independent sources of error, a proportional and an additive component, and the variance of the residual error is the sum of both components.

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- Method SD assumes one source of residual error, and the standard deviation of the residual error is the sum of a proportional and an additive component.

Both methods are described in detail below. NONMEM (Icon Development Solutions, Hanover, MD, USA) symbols and coding were used throughout this paper.

2.1.1. Method VAR.1

The combined proportional and additive residual error model is described in the NONMEM manual (Boeckmann et al., 2013) by the following code in the $ERROR block:

$$Y = F + F*EPS(1) + EPS(2) \quad (1)$$

where Y is the modelled value for the observed variable under the statistical model, F is the model predicted value, and EPS(1) and EPS(2) are random values from normal distributions N(0,SIGMA(1)) and N (0,SIGMA(2)), respectively.

Eq. (1) implies that the proportional and additive components are assumed to be statistically independent. The residual error, i.e., the difference between Y and F is explained by the sum of both independent components F*EPS(1) and EPS(2).

The standard deviation of the residual error, W, is obtained from the square root of the variance, which in turn is the sum of the variances of both components, resulting in:

$$W = SQRT(SIGMA(1)*F*F + SIGMA(2)) \quad (2)$$

and can be used to convert the residual to the weighted residual (IWRES) by dividing the residual by W (see below, Eq. (11)).

2.1.2. Method VAR.2

The following code may be used instead of Eq. (1):

$$Y = F + SD1*F*EPS(1) + SD2*EPS(2) \quad (3)$$

where SD1 and SD2 are model parameters (THETAs) that can be estimated by fixing the variances of EPS(1) and EPS(2) to 1 by

$$\$SIGMA\ 1\ FIX\ 1\ FIX \quad (4)$$

Using Eq. (3), the standard deviation W can be obtained from:

$$W = SQRT((SD1*F)**2 + SD2**2) \quad (5)$$

Although Eqs. (1) and (3) produce identical results (see Results section), the output provided by NONMEM is different. Eq. (1) provides estimates of SIGMA(1) and SIGMA(2), which can be converted to standard deviations SD1 and SD2 by:

$$SDn = (SIGMAn)^{0.5} \quad (6)$$

The corresponding standard errors can be obtained from the law of error propagation:

$$SE^2(SDn) = \left(\frac{\partial SDn}{\partial SIGMAn}\right)^2 \cdot SE^2(SIGMAn) \quad (7)$$

where the partial derivative is obtained from Eq. (6), resulting in $1/(2 \cdot SD_n)$, so Eq. (7) can be simplified to:

$$SE(SDn) = \left(\frac{1}{2 \cdot SDn}\right) \cdot SE(SIGMAn) \quad (8)$$

Eq. (3) provides THETA values for SD1 and SD2, with the corresponding standard errors. After rearrangement of Eqs. (6)–(8), the standard errors for the corresponding variances may be calculated.

2.1.3. Method VAR.3

Alternatively, since the standard deviation is given by Eq. (5), the model may be coded as:

$$Y = F + W*EPS(1) \quad (9)$$

Note that method VAR.3 (Eq. (9)) uses a single EPS (with $SIGMA 1 FIX), whereas methods VAR.1 (Eq. (1)) and VAR.2 (Eq. (3)) use two EPS values.

2.1.4. Method SD

Method SD assumes that the standard deviation of the residual error is the sum of the proportional and additive component. Therefore the standard deviation is modelled as a function of F according to:

$$W = SD1*F + SD2 \quad (10)$$

Using Eqs. (9) and (10), the error model may be coded with a single EPS (with $SIGMA 1 FIX).

2.2. Examples

2.2.1. Example 1

The datafile was obtained from the website of the American College of Clinical Pharmacology (no longer provided by this website), and can be found now at Certara Forum (2016). There were 100 subjects, given a dose of 100 or 250 mg, and each individual was sampled at 15 time points post-dose.

The pharmacokinetic model was a one-compartment model with clearance (*CL*) and volume of distribution (*V*) using subroutines ADVAN1 and TRANS2, with inter-individual variability in both parameters, assuming a log-normal distribution. Covariates were not used in the present analysis.

2.2.2. Example 2

The datafile was a modified version of the datafile of example 1, where the doses of 100 mg, as given to the first 50 patients, were changed to 150 mg, with a corresponding conversion of the observed concentrations (DV) by multiplying by 1.5, assuming linear pharmacokinetics.

2.3. Simulations

Simulated datasets were generated using each of the methods VAR.1, VAR.2, VAR.3 and SD, and analyzed using the same method as used for generation and using each of the other methods. For each example and each combination of methods, 1000 datasets were generated and analyzed. To allow a comparison of the methods for analysis with identical datasets, the seed for the random generator was the same in all simulations.

2.4. Calculations

The root mean squared error (RMSE) of the individual weighted residuals (IWRES) was calculated, where IWRES was obtained from:

$$IWRES = (DV–F)/W \quad (11)$$

All calculations were performed using NONMEM version 7.3.0 (Icon Development Solutions, Hanover, MD, USA. http://www.iconplc.com/innovation/nonmem/) using the first-order conditional estimation (FOCE) method with interaction. Nonparametric 95% confidence intervals were obtained by bootstrap analysis using PLT Tools version 5.5.0 (PLTsoft, San Francisco, CA. http://www.PLTsoft.com/) and R version 3.3.1 (R Foundation for Statistical Computing. https://www.R-project.org).

The methods and equations for combined proportional and additive residual error modelling are summarized in Table 1.

3. Results

3.1. Example 1

The results are summarized in Table 2. Methods VAR.1, VAR.2 and

Table 1
Overview of methods and equations.

Method	Equations	Number
VAR.1	W = SQRT(SIGMA(1)*F*F + SIGMA(2))	Eq. (2)
	Y = F + F*EPS(1) + EPS(2)	Eq. (1)
VAR.2	W = SQRT((SD1*F)**2 + SD2**2)	Eq. (5)
	Y = F + SD1*F*EPS(1) + SD2*EPS(2)	Eq. (3)
VAR.3	W = SQRT((SD1*F)**2 + SD2**2)	Eq. (5)
	Y = F + W*EPS(1)	Eq. (9)
SD	W = SD1*F + SD2	Eq. (10)
	Y = F + W*EPS(1)	Eq. (9)

VAR.3 yielded identical results, when for method VAR.1 the values of the correlation matrix of sigma (containing the sigma values as standard deviation in the diagonal; this is not explained in the NONMEM output or manuals) are used for SD1 and SD2, or by calculation of SD1 and SD2 using Eqs. (6)–(8). For comparison, the values of SIGMA(1) and SIGMA(2) were also calculated for methods VAR.2, VAR.3 and SD using Eqs. (6)–(8).

Comparing the results with methods VAR and SD, the following is observed:

i) The OFV is lowest for method SD; OFV is 6 units lower, with the same number of estimated parameters. Therefore method SD should be considered superior over method VAR in this dataset.
ii) The parameters describing residual error are markedly lower for method SD than for method VAR, and the 95% confidence intervals do not overlap. The standard errors of SD1 and SD2 are comparable for both methods.
iii) Typical values of the parameters, their inter-individual variance (OMEGA) and the corresponding standard errors are comparable, but not identical for both models. The differences do not seem relevant from a practical and clinical point of view.
iv) Epsilon shrinkage is comparable for both models. In both cases the epsilon shrinkage provided by NONMEM agrees with the calculated value of 1 – RMSE(IWRES), confirming the correctness of the calculated IWRES.
v) Diagnostic plots, including IWRES versus posthoc predicted concentrations, were quite similar for both methods, showing the expected normal distribution, with IWRES values within the range of −3 to +3.

To explore the difference between methods VAR and SD, the relationship between concentration (F) and standard deviation (W) according to methods VAR and SD is plotted in Fig. 1. The profiles are different: (1) for method SD there is a linear relationship between concentration and standard deviation, whereas this relationship is non-linear for method VAR; (2) for concentrations below 10 mg/L and above 39 mg/L the standard deviation for method SD is lower than that for method VAR, whereas for intermediate concentrations the standard deviation for method SD is higher than that for method VAR. In the example dataset, the percentage of concentrations below 10 mg/L is 32%, above 39 mg/L 18% and between 10 and 39 mg/L 50%.

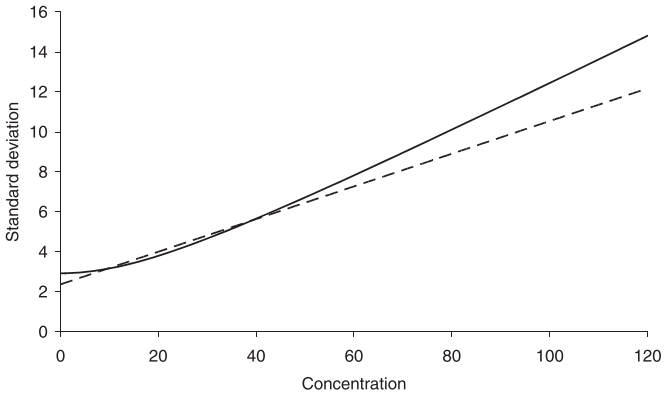

Fig. 1. Relationship between concentration (F) and standard deviation (W) according to method VAR (Eq. (5), solid line) and method SD (Eq. (10), dashed line) for example 1, calculated from the equations in Table 1 and parameters SD1 and SD2 given in Table 2.

Both combined proportional and additive residual error methods VAR and SD resulted in a significant better fit than a proportional model (OFV 6299) or an additive model (OFV 6559).

3.2. Example 2

The results for example 2 are summarized in Table 3. OFV is lowest for method VAR. For both methods, the parameter SD1 is lower than for example 1 and SD2 is higher.

As shown in Fig. 2, for concentrations below 13 mg/L and above 47 mg/L the standard deviation for method SD is lower than that for method VAR, whereas for intermediate concentrations the standard deviation for method SD is higher than that for method VAR. In the example dataset, the percentage of concentrations below 13 mg/L is 32%, above 47 mg/L 8% and between 13 and 47 mg/L 60%.

Both combined proportional and additive residual error models resulted in a significant better fit than a proportional model (OFV 6775) or an additive model (OFV 7167).

Table 2
Example 1: results of the NONMEM analysis (standard error) [95% confidence interval].

	Method VAR		Method SD	
OFV	6046.462		6040.320	
CL (L/h)	0.417 (0.020)	[0.379–0.455]	0.418 (0.020)	[0.381–0.456]
V (L)	7.16 (0.32)	[6.54–7.82]	7.17 (0.32)	[6.55–7.79]
OMEGA(*CL*)	0.171 (0.025)	[0.126–0.222]	0.174 (0.026)	[0.126–0.225]
OMEGA(*V*)	0.198 (0.027)	[0.145–0.252]	0.199 (0.027)	[0.145–0.255]
SIGMA(1) proportional error	0.0147 (0.0016)[a]		0.00668 (0.00100)[b]	
SIGMA(2) additive error (mg^2/L^2)	8.57 (0.60)[a]		5.62 (0.53)[b]	
SD1 proportional error	0.121 (0.007)[c]	[0.108–0.134]	0.0817 (0.0061)	[0.0695–0.0933]
SD2 additive error (mg/L)	2.93 (0.10)[c]	[2.71–3.11]	2.37 (0.11)	[2.15–2.58]
EPS shrinkage[d]	0.0595		0.0600	
RMSE(IWRES)[e]	0.9405		0.9400	

[a] Obtained using method VAR.1 or using method VAR.2 or VAR.3 and Eqs. (6)–(8).
[b] Obtained using method SD and Eqs. (6)–(8).
[c] Obtained using method VAR.2 or VAR.3, or using method VAR.1 and Eqs. (6)–(8).
[d] Reported by NONMEM.
[e] Calculated from Eq. (11).

Table 3
Example 2: results of the NONMEM analysis (standard error) [95% confidence interval].

	Method VAR		Method SD	
OFV	6662.656		6665.335	
CL (L/h)	0.416 (0.020)	[0.378–0.455]	0.417 (0.020)	[0.380–0.456]
V (L)	7.15 (0.32)	[6.54–7.78]	7.15 (0.32)	[6.55–7.80]
OMEGA(*CL*)	0.172 (0.027)	[0.124–0.224]	0.175 (0.027)	[0.126–0.228]
OMEGA(*V*)	0.201 (0.027)	[0.150–0.258]	0.201 (0.027)	[0.147–0.256]
SIGMA(1) proportional error	0.0106 (0.0015)[a]		0.00371 (0.00090)[b]	
SIGMA(2) additive error (mg^2/L^2)	15.9 (1.0)[a]		11.6 (1.1)[b]	
SD1 proportional error	0.103 (0.007)[c]	[0.088–0.116]	0.0609 (0.0074)	[0.0450–0.0749]
SD2 additive error (mg/L)	3.98 (0.12)[c]	[3.73–4.21]	3.41 (0.17)	[3.09–3.73]
EPS shrinkage[d]	0.0595		0.0599	
RMSE(IWRES)[e]	0.9405		0.9401	

[a] Obtained using method VAR.1 or using method VAR.2 or VAR.3 and Eqs. (6)–(8).
[b] Obtained using method SD and Eqs. (6)–(8).
[c] Obtained using method VAR.2 or VAR.3, or using method VAR.1 and Eqs. (6)–(8).
[d] Reported by NONMEM.
[e] Calculated from Eq. (11).

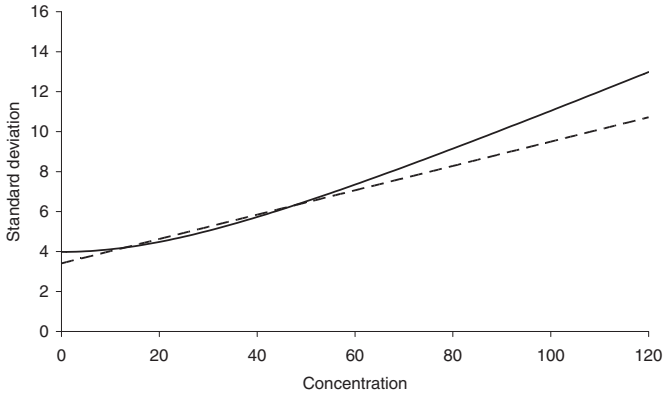

Fig. 2. Relationship between concentration (F) and standard deviation (W) according to method VAR (Eq. (5), solid line) and method SD (Eq. (10), dashed line) for example 2, calculated from the equations in Table 1 and parameters SD1 and SD2 given in Table 3.

3.3. Simulations Example 1

First, it was confirmed that the datasets generated using method VAR.1 and VAR.2 are identical. Method VAR.3 yields different datasets due to the use of a single random number in contrast to methods VAR.1 and VAR.2, which use two random numbers. However, the datasets have the same statistical characteristics.

Second, using methods VAR.1, VAR.2 and VAR.3 during analysis resulted in virtually identical results, with some irrelevant differences for method VAR.1, probably due to the use of variances (SIGMA) instead of standard deviations as estimated parameters (THETA) in the NONMEM analysis. Therefore only the results for method VAR.2 are presented here.

The results of the simulations are summarized in Table 4. The median OFV value was lowest when the data were analyzed using the same method as used for data generation; the median difference between OFV using the same method for analysis and using the other method was about 6 units for data sets generated with either method VAR or method SD.

For data sets generated with method VAR, OFV with method SD was lower in 13.4% of the datasets. For data sets generated with method SD, OFV with method VAR was lower in 13.6% of the datasets.

For both methods, *CL* was overestimated by about 1%, and the inter-individual variability in *CL* and *V* was underestimated by about 5% and 3%, respectively. The differences between estimates of the structural parameters *CL* and *V* and their variances using methods SD and VAR for analysis were small, i.e. less than 1%.

The values for SD1 and SD2 were close to the values used for simulation if the same method was used for analysis (Table 4); if the other method was chosen, the values of SD1 and SD2 deviated from the value used for simulation, in accordance with the differences shown in Table 2. It should be noted that this difference is due to the different interpretation of SD1 and SD2, and do not imply that 'the other method' results in imprecise parameters; it was confirmed that in all cases the actual residual error of both methods were close to each other.

3.4. Simulations Example 2

The results are summarized in Table 5. The results were comparable to that obtained with example 1. For data sets generated with method VAR, OFV with method SD was lower in 19.9% of the datasets. For data sets generated with method SD, OFV with method VAR was lower in 21.4% of the datasets.

Table 4
Results of simulations with example 1. Values are median values (% error) of 1000 simulated datasets similar to example 1. Parameters used for data generation and equations used for data generation and data analysis are given in Table 2.

Data generation Data analysis	Method VAR Method VAR	Method VAR Method SD	Method SD Method SD	Method SD Method VAR
OFV	5997	6002	5990	5996
CL	0.423 (+1.4)	0.424 (+1.7)	0.425 (+1.7)	0.424 (+1.4)
V	7.17 (+0.1)	7.17 (+0.1)	7.17 (−0.0)	7.18 (+0.7)
OMEGA(*CL*)	0.161 (−5.8)	0.162 (−5.6)	0.166 (−4.6)	0.165 (−5.2)
OMEGA(*V*)	0.192 (−3.0)	0.193 (−2.5)	0.193 (−3.0)	0.192 (−3.5)
SD1	0.121 (+0.0)	0.0740 (−39)	0.0814 (−0.4)	0.128 (+57)
SD2	2.94 (+0.3)	2.50 (−15)	2.37 (+0.0)	2.85 (+20)

Table 5
Results of simulations with example 2. Values are median values (% error) of 1000 simulated datasets similar to example 2. Parameters used for data generation and equations used for data generation and data analysis are given in Table 3.

Data generation Data analysis	Method VAR Method VAR	Method VAR Method SD	Method SD Method SD	Method SD Method VAR
OFV	6625	6628	6628	6630
CL	0.421 (+1.2)	0.422 (+1.4)	0.422 (+1.2)	0.421 (+1.0)
V	7.16 (+0.1)	7.16 (+0.1)	7.16 (+0.1)	7.16 (+0.1)
OMEGA(*CL*)	0.161 (−6.4)	0.162 (−5.8)	0.167 (−4.6)	0.166 (−5.1)
OMEGA(*V*)	0.196 (−2.5)	0.196 (−2.5)	0.196 (−2.5)	0.195 (−3.0)
SD1	0.103 (+0.0)	0.0529 (−49)	0.0610 (+0.2)	0.111 (+82)
SD2	3.98 (−0.0)	3.56 (−11)	3.41 (+0.0)	3.89 (+14)

4. Discussion

In example 1, the lower OFV for method SD shows that, for this data set, method SD is superior over method VAR. So, in spite of the widespread application of method VAR, this approach does not guarantee the solution with the lowest OFV.

Interestingly, the number of EPS values is not an essential characteristic of the methods; method SD uses one EPS value, but method VAR can be applied with two EPS values (method VAR.1 and VAR.2) and with one EPS value (method VAR.3), yielding identical results.

The essential difference between the methods is the assumption with respect to the relationship between the variable (Y) and its standard deviation (W).

Method VAR assumes two independent sources of error, a proportional and an additive component, and the variance of the residual error is the sum of both components, resulting in a standard deviation given by Eq. (2) or (5):

$$\text{Method VAR:} \quad \text{variance} = (SD1 \cdot F)^2 + SD2^2 \tag{12}$$

Method SD assumes one source of residual error, and the standard deviation of the residual error is the sum of a proportional and an additive component, as described in Eq. (10) and depicted in Figs. 1 and 2, where method SD shows a straight line:

$$\text{Method SD:} \quad \text{standard deviation} = SD1 \cdot F + SD2 \tag{13}$$

Although the two methods assume a different underlying mechanism of the sources of error, it is usually not known which mechanism is more likely. Therefore both assumptions are plausible, and there is no apparent reason for a priori preference for one assumption over the other. As concluded from discussions on internet (NONMEM Users Network, 2001; PharmPK Discussion, 2013), Method VAR is routinely used by users of NONMEM and Phoenix WinNonlin (Certara, Princeton, New Jersey. https://www.certara.com/software/pkpd-modeling-and-simulation/phoenix-winnonlin/), whereas Method SD is applied in software from the Laboratory of Applied Pharmacokinetics and Bioinformatics (University of Southern California, Los Angeles. http://www.lapk.org/) and in MwPharm (Mediware a.s. http://www.mediware.cz/). Phoenix WinNonlin uses a parameter CMixRatio for the ratio of SD1/SD2 (PharmPK Discussion, 2013). This approach is not recommended since this parameter has no meaning by itself, being the ratio of both error components, with a different meaning and unit, thus obscuring the actual meaning of parameters.

The simulations demonstrate that the method for data generation, i.e. the assumptions about the relationship between residual error and its standard deviation, is preserved in the data, since in most datasets a lower OFV was found using the same method for data generation and analysis.

A limitation of the current study is that it is not yet clear what factors could result in large differences between the evaluated methods, for example: study design, bioanalysis and pharmacokinetic model. Another limitation is that it is not yet known how both methods compare in the case of special procedures for values below the quantification limit of the assay (Ahn et al., 2008).

For many practical purposes the difference between both methods is hardly relevant, given the close agreement in model parameters, except for SD1 and SD2, between both models. The values of SD1 and SD2 with method SD are always lower than with method VAR. However, this should not be interpreted as a lower residual error in method SD; the actual residual error in both methods is close to each other. Although the choice of the method does not seem to be critical, it should be noted that, when the result of an analysis is used for simulation purposes, it is essential that the simulation tool uses the same method as used during analysis. Mixing up the methods in analysis and simulation will lead to under- or overestimation of residual variability in the simulated data.

In conclusion, both methods are valid approaches in combined proportional and additive residual error modelling, and selection may be based on the OFV.

Conflicts of Interest

The author has no conflicts of interest to declare. No funding was received in the preparation of this article.

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